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BRIEF COMMUNICATION

Immune checkpoint inhibitors in the onset of myasthenia gravis with hyperCKemia

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Abstract

Immune checkpoint inhibitors sometimes cause neuromuscular adverse events. Although a few cases of myasthenia gravis with hyperCKemia triggered by immune checkpoint inhibitors have been described, conclusive evidence remains limited. We conducted a systematic review of published cases of myasthenia gravis with hyperCKemia related to immune checkpoint inhibitors. Moreover, we tested anti-striational antibodies in the case of myasthenia gravis with myositis after nivolumab administration. We located 17 published case reports. Anti-striational antibodies were tested in six cases and five cases were positive. Our systematic analyses revealed poor prognosis in myasthenia gravis combined hyperCKemia with immune checkpoint inhibitors.

Introduction

Immune checkpoint inhibitors (ICIs) are therapeutic monoclonal antibodies (mAbs) with immunomodulatory activity that have been shown to improve the overall survival of patients with several types of malignancy.[1] The exact mechanisms of tumor regression triggered by the two clinically tested mAbs against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1), as well as the mechanisms related to their adverse effects, are under investigation.[2–4] Evidence of adverse autoimmune reactions caused by ICIs has been accumulating, and some studies have reported new-onset autoimmune diseases after pharmacotherapy with ICIs. By unbalancing the immune system, these new immunotherapeutic agents also generate dysimmune toxicities, called immune-related adverse events (IRAEs), such as in the nervous system, gastrointestinal tract, skin, endocrine glands, and lung, but may affect any tissue.[5] From a clinical perspective, management of IRAEs caused by ICIs requires close collaboration of oncologists and other clinical specialists. Such collaboration may also provide new insights into the pathophysiology of neuroimmunological diseases, such as myasthenia gravis (MG) and Guillain–Barré syndrome.[6,7] As physicians, we should be aware of the potential for ICI-triggered dysimmune toxicities associated with antitumoral responses.

Here, we review previous reports of ICI-induced MG with hyperCKemia cases to evaluate and compare the clinical manifestations of patients during and after ICI treatment. In addition, we discuss the effect of blocking the pathway for PD-1 and its ligand (PD-L1) on the production of autoantibodies against neuromuscular junction and muscle, through a process mediated by both T cells and B cells.

Methods

We conducted a detailed systematic review of published cases of MG with hyperCKemia that developed during or after ICI treatment. We utilized Google Scholar and PubMed for our search that targeted relevant peer-reviewed articles, via the following medical subject heading terms: myasthenia gravis, neuromuscular disease/disorder, myopathy, myositis, CTLA-4 antibody, PD-1 antibody, ipilimumab, nivolumab, and pembrolizumab. We searched the reference lists found in relevant articles and textbooks manually. We extracted and tabulated data including age at onset of MG and of malignancy, sex, time between ICI treatment and MG onset, initial MG symptoms, MG symptoms during the entire course of medication, myalgia, hyperCKemia, myocarditis, changes in anti-acetylcholine receptor (AChR) antibody levels, the presence of anti-striational antibody, MG treatment, MGFA classification, and clinical outcome.

Moreover, we tested for serum antibodies to MuSK, lipoprotein receptor-related protein 4 (LRP4), and ganglionic AChR, as measured by the luciferase immunoprecipitation system; for antibodies to signal recognition particle (SRP), 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), and titin antibodies, as assessed by an enzyme-linked immunosorbent assay (ELISA)[8–10] in the case previously reported by Kimura et al.[11] Furthermore, anti-muscular voltage-gated potassium channel (Kv1.4) antibodies were measured by an immunoprecipitation assay.[12]

Results

We obtained data for 17 cases of ICI therapy followed by MG with hyperCKemia or anti-striational antibody, as shown in Table 1.[11,13–28] The patients in 15 cases had hyperCKemia and the patients in four of these cases complained of myalgia. Two studies did not report on hyperCKemia but the patients were positive for the anti-striational antibody. The anti-AChR antibodies were examined at MG onset in all patients and 14 were positive. In three patients, including one diagnosed with MG before ICI treatment, the anti-AChR antibody titer was assessed in serum samples obtained before and after ICI administration. These patients tested positive for the antibody before ICI administration and the titer increased after the onset of MG, which suggests that it predicted MG development before and during the ICI treatment (Tables 1, 2, and 3).

In the case previously reported by Kimura et al.,[11] who performed muscle biopsy, the diagnosis of myositis was confirmed by infiltration of inflammatory cells. Dyssynchrony of the left ventricle and apex, revealed by echocardiography, was considered as autoimmune myocarditis. The patient in that case was administered steroid pulse therapy followed by oral prednisolone. He also underwent plasmapheresis and was administered intravenous immunoglobulin. After these interventions, the symptoms in the respiratory muscles, proximal limbs, and bilateral ptosis improved and the level of anti-AChR antibodies decreased to 3.3 nmol/L. The patient had negative results for antibodies to MuSK, LRP4, and ganglionic AChR and for SRP and HMGCR antibodies. However, the anti-striational antibodies, anti-titin and Kv1.4, were both positive (Table S1). The presence of anti-striational antibodies in ICI-induced MG with hyperCKemia was detected in six patients; five patients were positive (Tables 1 and 2).

All the patients developed MG symptoms no later than the fourth dose of ICIs administration. Immunosuppressive therapy was administered in all patients; symptoms improved in seven, but 10 patients died despite intensive therapy. In eight of the 10 patients, MG was reported as the direct cause of death. Three of the deceased developed MG after the first administration of ICI and had severe respiratory failure, requiring intubation. The patients developed MG within 16 days or earlier and died within 4 weeks after the first dose of ICI treatment. In five patients, ICI treatment was deemed effective against cancer. Two patients continued ICI administration, despite developing MG, because it was highly effective.

Discussion

We identified 17 patients with MG with hyperCKemia or anti-striational antibody associated with ICIs, and 14 patients had respiratory failure or worsening of MG symptoms shortly after ICI-induced MG onset. In view of the rapid onset and severity of the disease, which can be fatal, anti-AChR and anti-striational antibodies should be routinely measured before the start of ICI therapy. We described a case of new-onset MG triggered by ICI therapy that was associated with myasthenic crisis, myositis, and myocarditis.[11] We may have observed the very early stage of fulminant MG, as the patient was only partially placed on artificial ventilation for the first few days after onset. The patient had positive test results for anti-AChR and anti-striational antibodies, which are associated with

Table 1. Detailed clinical features of patients with myasthenia gravis (MG) with hyperCKemia or anti-striational antibody associated with Nivolumab.

Variable	Nivolumab									
Author, year, reference	Lopez et al., 2015[13]	Shirai et al., 2016[14]	Maeda et al., 2016[15]	Kimura et al., 2016[11]	Chang et al., 2017[16]	Tan et al., 2017[17]	Chen et al., 2017[18]	Konoeda et al., 2017[19]	Mehta et al., 2017[20]	Mitsune et al., 2018[21]
Age at MG onset, y	ND	81	50	80	75	45	65	74	73	47
Age at malignancy onset, y	65	78	76	79	66	45	64	74	69	62
Sex	M	F	M	M	M	M	M	F	M	F
Malignancy	RCC	Melanoma	Melanoma	Melanoma	SCC of bladder	NSCLC	SCLC	Colon cancer	RCC	Neuroendocrine carcinoma
Diagnosed with MG before ICIs use	No	No	Ocular MG	No	No	No	No	No	No	Ocular MG
MG treatment before ICIs use	–	–	Oral PSL	–	–	–	–	–	–	–
ICIs infusions before MG onset	2	1	3	1	2	1	3	2	2	2
Initial symptoms of MG	Dyspnea, diplopia, ptosis,	Fatigue, proximal limb weakness	Diplopia, dysphagia, facial weakness	Fatigue, muscle weakness	Fatigue, generalized weakness	Dyspnea	Limb weakness	Ptosis	Weakness in limbs, dyspnea	General fatigue, muscle weakness
MG symptoms during entire course of disease	Muscular weakness, back pain	Dyspnea, ptosis, diplopia	ND	Dyspnea, ptosis	Dysphagia, severe shortness of breath	Ptosis, ophthalmoplegia	Ptosis, diplopia, drop head, dysphagia, dyspnea	Diplopia, Limb and neck weakness, dyspnea	ND	Ptosis, dyspnea
Myalgia	ND	+	–	–	ND	ND	ND	+	+	ND
HyperCKemia	+	+	+	+	+	+	+	+	+	+
Myocarditis	ND	–	ND	+	ND	–	–	–	ND	±
Max CK U/L	6,321	8,729	1,627	7,740	1,587	ND	2,216	5,331	8,950	14,229
Anti-AChR Abs before ICI use, nmol/L	ND	2.9	15.2	10.2	ND	ND	ND	ND	ND	ND
Anti-AChR Abs at MG onset, nmol/L	98	12.4	20.0	28.0	2.28	2.0	–	0.3	8.70	0.6
Anti-AChR Abs after immunotherapy, nmol/L	ND	ND	ND	3.3	ND	ND	ND	< 0.2	ND	ND
Anti-striational antibody	–	ND	ND	+	ND	ND	ND	ND	ND	ND
Required mechanical ventilation	Refused	Declined	–	+	NPPV	+	Declined	NPPV	+	–
MGFA classification	IVb	IVb	IIb	V	IVb	IVb	IVb	IVb	V	IIIb
Outcome of clinical course	Died	Died	Improved	Improved	Died	Improved	Died	Improved	Improved	Improved
Cause of Death	MG	MG			MG		MG			
Onset of MG to death	18 days	14 days			20 days		22 days			

Anti-AChR Abs, anti-acetylcholine receptor antibodies; CK, creatine kinase; NSCLC, non-small-cell lung cancer; ND, not described in the case report; SCC, squamous cell carcinoma; SCLC, small-cell lung cancer; F, female; M, male.

Table 2. Detailed clinical features of patients with myasthenia gravis (MG) with hyperCKemia or anti-striational antibody associated with ipilimumb or ipilimumab and nivolumab or pembrolizumab.

Variable	Ipilimumab	Ipilimumab + nivolumab		Pembrolizumab			
Author, year, reference	Liao et al., 2014[22]	Loochtan et al., 2015[23]	Chen et al., 2017[24]	Zimmer et al., 2016[25]	Gonzalez et al., 2017[26]	Earl et al., 2017[27]	March et al., 2018[28]
Age at MG onset, y	71	70	57	69	71	62	63
Age at malignancy onset, y	70	69	57	ND	71	74	ND
Sex	F	M	M	F	F	M	M
Malignancy	Melanoma	SCLC	NSCLC	Melanoma	UCS	Melanoma	Melanoma
Diagnosed with MG before ICIs use	No	No	No	No	No	No	No
MG treatment before ICIs use	–	–	–	–	–	–	–
ICIs infusionsbefore MG onset	3	1	1, 2	3	4	2	1
Initial symptoms of MG	Dysphagia, odynophagia	Ptosis, diplopia	Ptosis, dyspnea, muscle weakness	Movement disorder of eyes, ptosis, dyspnea	Dysphagia, diplopia	Ptosis, diplopia	Ptosis, diplopia, dyspnea
MG symptoms during entire course of disease	Ptosis, neck weakness, proximal limb weakness	Dyspnea, general weakness	Polyneuropathy	General weakness	Dysarthria, neck weakness, proximal muscle weakness	Dysphagia, dyspnea, l imb weakness	Progressive facial weakness
Myalgia	+	ND	ND	ND	ND	ND	ND
HyperCKemia	+	ND	+	+	+	ND	+
Myocarditis	ND	ND	ND	ND	ND	ND	–
Max CK U/L	1,268	ND	2682	ND	1,200	ND	10,386
Anti-AChR Abs before ICI use, nmol/L	ND	ND	ND	ND	ND	ND	ND
Anti-AChR Abs at MG onset, nmol/L	2.09	1.64	0.7	–	–	6.79	+
Anti-AChR Abs after immunotherapy, nmol/L	ND	ND	ND	ND	–	ND	ND
Anti-striational antibody	+	+	ND	+	ND	+	ND
Required mechanical ventilation	–	+	–	–	–	–	+
MGFA classification	IIIb	V	IIIb	IVb	IIb	IVb	V
Outcome of clinical course	Improved	Died	Died	Died	Died	Died	Died
Cause of Death		MG	Sepsis	MG	Malignancy	MG	MG
Onset of MG to death		22 days	ND	4 months	5 months	ND	14 days

Anti-AChR Abs, anti-acetylcholine receptor antibodies; ChEIs, cholinesterase inhibitors; CK, creatine kinase; ICI, immune checkpoint inhibitors; IVIg, intravenous immunoglobulin; MGFA, Myasthenia Gravis Foundation of America; NSCLC, non-small-cell lung cancer; ND, not described in the case report; PSL, prednisolone; SCLC, small-cell lung cancer; UCS, uterine carcinosarcoma; F, female; M, male.

Table 3. Therapeutic features of patients with myasthenia gravis (MG) with hyperCKemia or anti-striational antibody associated with immune checkpoint inhibitor (ICI) treatment.

Variable, No.	Nivolumab, 10	Ipilimumab + Nivolumab, 2	Ipilimumab, 1	Pembrolizumab, 4
MG treatment before ICIs use, No. (%)	1 (10)	0 (0)	0 (0)	0 (0)
Treatments, No. (%)				
Steroid pulse	6 (60)	2 (100)	1 (100)	2 (50)
IVIg	7 (70)	2 (100)	1 (100)	2 (50)
Plasmapheresis	3 (30)	1 (50)	1 (100)	2 (50)
Oral PSL	8 (80)	1 (50)	0 (0)	4 (100)
Immunosuppressant	0 (0)	0 (0)	0 (0)	1 (25)
ChEIs	6 (60)	1 (50)	1 (100)	4 (100)
ICIs use after MG, No. (%)	1 (10)	0 (0)	0 (0)	1 (25)
ICI efficacy, No.	4	ND	ND	1

ChEIs, cholinesterase inhibitors; IVIg, intravenous immunoglobulin; ND, not described in the case report; PSL, prednisolone.

the onset of MG and myositis/myocarditis, respectively. One case report of ICI-induced MG without hyperCKemia was negative for anti-striational antibodies.[29] In contrast, Bielen reported anti-striational antibody-positive severe polymyositis after combination therapy with ipilimumab and nivolumab.[30] The patient additionally had ptosis and extraocular muscle weakness, which suggest complication of MG. Five patients with ICI-induced MG were positive for anti-striational antibodies. All had severe symptoms (three of them died and one required permanent ventilation); assessing for anti-striational antibodies before ICI therapy might have predicted the fulminant MG with myositis. Previous reports have described inflammatory myopathies and myocarditis in patients with MG. Suzuki et al.[31] found anti-striational antibodies in seven of 924 patients with MG had myositis and/or myocarditis (0.8%). They concluded that some patients with MG have heart and skeletal muscles that are autoimmune targets and they suggested that this autoimmunity can be found along a broad clinical spectrum with anti-striational antibodies in patients with MG. MG is rare side effect of ICIs, though the incidence of hyperCKemia or anti-striational-positive MG seems to be high than ordinary MG. Although we reviewed only a small number of ICI-induced MG case reports of patients with hyperCKemia or who were positive for anti-striational antibodies, in future study, we should compare the prognosis of patients with ICI-induced MG with or without anti-striational antibodies. Blockade of the PD-1/PD-L1 pathway may increase autoantibody production against neuromuscular junctions, skeletal muscle, and cardiac muscle. Studies with PD-1-deficient mice have shown the development of autoimmune cardiomyopathy.[32] Although anti-striational antibodies have no bearing on autoimmune cardiomyopathy, Okazaki et al.[33] identified autoantibodies against cardiac troponin I in PD-1-deficient mice with dilated cardiomyopathy. They showed that autoantibodies impair heart function by binding to cardiac troponin I on the cardiomyocyte surface.

With regard to experimental autoimmune MG (EAMG), Wang et al.[34] demonstrated that anti-CTLA-4 antibody treatment enhanced the T-cell response to AChR, increased the production of anti-AChR antibodies, and induced clinical EAMG in terms of onset and severity. We expect that the mechanisms of ICI-induced MG were similar to the immune response mechanisms in this EAMG study. ICI treatment most likely enhances the ability of autoreactive T cells to help B cells. The enhanced B-cells function as antibody-producing cells or as antigen-presenting cells and may contribute to features of disease development, such as rapid onset and exacerbation.

PD-1 and CTLA-4 are critical inhibitors that contribute to prevention of B-cell-mediated autoimmune disease. Self-tolerance is maintained partly by inhibition of autoreactive T cells through the CTLA-4 and PD-1/PD-L1 axes.[35,36] Polymorphisms in PD-1 and CTLA-4 are associated with various autoimmune conditions such as thyroid diseases, diabetes, systemic lupus erythematosus, and rheumatoid arthritis.[37] In a previous study, a genome-wide association study of MG showed a significant association between CTLA4 and MG.[38] Moreover, Hong et al. reported a genetic association of CTLA4 in juvenile-onset MG in China.[39] Some of these autoimmune diseases share clinical features with IRAEs caused by ICI treatment.[40–42] Nevertheless, given the increasing use of ICIs across a spectrum of oncological diseases and the recent approval of ipilimumab in combination with nivolumab for patients with melanoma, studies to determine the incidence of autoimmune conditions such as MG among

patients with cancer receiving ICI therapy are warranted. As ICIs are increasingly used in the clinic, constant monitoring is important for potential IRAEs during ICI treatment.

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Author Contributions

TK, SF, TK, AM, SY, MJ, HI, and YA examined the patients; KT, SN, SS, AM, KW, and YK performed the laboratory tests; KT, SN, TK, and SF summarized the cases; KT, SN, SS, SF, and YK analyzed the data; KT, SN, SS, TK, SF, YK, HI, NS, and YA wrote the paper.

Conflict of Interest

All authors have no conflicts of interest to disclose.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Profiles of autoantibodies before and after anti-PD-1 treatment in our case

